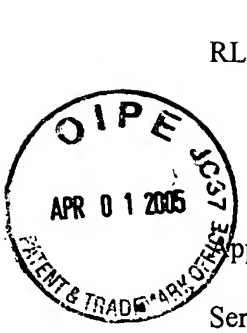
RLL-297US

IFW



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	KHANNA *et al.*	Atty. Dkt. No.:	RLL-297US
Serial No.:	10/690,897	Group Art Unit:	1625
Filing Date:	October 22, 2003	Examiner:	Patricia L. Morris
Title:	AMORPHOUS FORM OF ESOMEPRAZOLE SALTS		

Certificate of Mailing

I certify that this correspondence is being deposited with the United States Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 24, 2005.

Kim Campbell

Kim Campbell

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 1057/Del/2002 filed 22 October 2002 (22.10.2002) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: William D. Hare

William D. Hare, Esq.
Senior Counsel – Intellectual Property
Reg. No. 44,739

Dated: March 24, 2005
Ranbaxy Inc.
600 College Road East, Suite 2100
Princeton, New Jersey 08540
Tel.: 609-720-5608
Fax: 609-514-9779

INTELLECTUAL PROPERTY **INDIA**

सत्यमेव जयते

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Complete Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1057/Del/2002 dated 22nd October 2002.***

Witness my hand this 22nd day of February 2005.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

CERTIFIED COPY OF
PRIORITY DOCUMENT

FORM 1

22 OCT 2002

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"PREPARATION OF AMORPHOUS FORM OF ESOMEPRAZOLE MAGNESIUM"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. MAHAVIR SINGH KHANNA

b. BAKTHAVATHSALAN VIJAYARAGHAVAN

c. MOHAN PRASAD

d. YATENDRA KUMAR

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

6. Following declaration was given by the inventors in the convention country:

We, MAHAVIR SINGH KHANNA, BAKTHAVATHSALAN VIJAYARAGHAVAN MOHAN PRASAD, YATENDRA KUMAR of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (MAHAVIR SINGH KHANNA)

b. (BAKTHAVATHSALAN VIJAYARAGHAVAN)

c. (MOHAN PRASAD)

d. (YATENDRA KUMAR)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **684627** dated **23.09.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **18th** day of **October,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

FORM 2

22 OCT 2009

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

PREPARATION OF AMORPHOUS FORM OF ESOMEPRAZOLE MAGNESIUM

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a novel amorphous form of the magnesium salt of the (-) enantiomer of omeprazole i.e. esomeprazole magnesium. The invention also relates to processes for preparing amorphous esomeprazole magnesium and pharmaceutical compositions comprising it.

US Patent No. 5714505 describes alkaline salts of the (-) enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridiniyl)methyl]sulfinyl]-1H-benzimidazoles i.e. esomeprazole including the magnesium salt, which are used for inhibiting gastric acid secretion. Esomeprazole magnesium is prepared according to this patent in optically pure crystalline form by precipitation / crystallization (Examples 5,6 and 7).

US 6124464 gives another process for preparing crystalline esomeprazole magnesium. US 6369085 discloses three different types of crystalline esomeprazole magnesium viz. dihydrate form A, dihydrate form B and the trihydrate form. However, there is no teaching of an amorphous form of esomeprazole magnesium in the known prior art.

It is known that different morphs of biologically active compounds may have different absorption profile in vivo and consequently different pharmacokinetic profile.

The present invention relates to a new form of esomeprazole magnesium, the amorphous form. The new form is characterized by its X-ray powder diffraction spectrum and IR spectrum as shown in Figures 1 and 2 of the accompanied drawings.

Pharmaceutical compositions of amorphous form of esomeprazole magnesium in admixture with a solid or liquid pharmaceutical diluent or carrier can be employed for treatment of gastric acid related diseases by inhibition of gastric acid secretion.

The present invention provides a process for the preparation of amorphous form of esomeprazole magnesium which comprises recovering amorphous esomeprazole magnesium from a solution thereof in a suitable solvent by spray drying.

The solution of esomeprazole magnesium may be obtained by dissolving crystalline esomeprazole magnesium in a suitable solvent or alternatively such a solution may be obtained directly, from a reaction in which esomeprazole magnesium is formed.

The term "suitable solvent" includes any solvent or solvent mixture in which esomeprazole magnesium is soluble such as alcohols, halogenated hydrocarbons, nitriles, cyclic ethers, and mixture(s) thereof. Examples of alcohols include methanol, ethanol, isopropanol, and the like. Examples of halogenated hydrocarbons include dichloromethane, dichloroethane, dibromoethane, and the like. Example of nitrile include acetonitrile and the like. Examples of cyclic ethers include tetrahydrofuran, dioxane, and the like.

An organic amine or ammonia may optionally be added to the solution of esomeprazole magnesium before spray drying. The organic amine may be diethylamine, triethylamine, and the like.

Crystalline esomeprazole magnesium used as a starting material may be any of the various polymorphic forms known in the prior art such as dihydrate form A, dihydrate form B, trihydrate etc.

Esomeprazole magnesium may be prepared by any of the known methods such as those cited in the patents US 5714504, US 6124464, and US 6369085. A solution of esomeprazole magnesium obtained in situ during the preparation process may be used as such for spray drying.

The spray drying may be accomplished using a spray dryer, which operates on the principle of nozzle spraying in a parallel flow, i.e. the sprayed product and the drying gas flow in the same direction. The drying gas can be air or inert gases such as nitrogen, argon or carbon dioxide.

The amorphous form of esomeprazole magnesium may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. and in these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients. In addition to the common dosage forms set

out above, the amorphous form of esomeprazole magnesium may also be administered by controlled release means and/or delivery devices.

The invention also relates to a method for treatment of gastric acid related diseases, comprising administering to a mammal in need of treatment a therapeutically effective amount of amorphous form of esomeprazole magnesium.

The present invention is further illustrated by the following examples which are however, not intended to limit the scope of the invention.

Preparation of amorphous form of esomeprazole magnesium

Example 1

Esomeprazole magnesium trihydrate (200g) was dissolved in a mixture of dichloromethane (1200ml) and methanol (1200ml) at 25-30°C. Any undissolved material was filtered off and triethylamine (2 ml) was added to the filtrate. The clear solution thus obtained was subjected to spray drying in a mini spray dryer (Model Buchi – 190) with an inlet temperature of 65-68°C and an outlet temperature of 22-42°C in 2 to 3 hours. The solid was further dried under vacuum at 60-65°C for 14 to 15 hours to yield 120 g of esomeprazole magnesium of amorphous form. X-ray powder diffraction pattern showed a plain halo which demonstrates amorphous nature of the product (Figure I). Purity 99.77% by HPLC, Chiral purity 99.90 % by HPLC, SOR:145.9°. Mg content 3.4.

Example 2

Esomeprazole magnesium trihydrate (20g) was dissolved in methanol (200ml) at 25-30°C. Any undissolved material was filtered off and triethylamine (0.2 ml) was added to the filtrate. The clear solution thus obtained was subjected to spray drying with an inlet temperature of 65-68°C and an outlet temperature of 22-42°C. The solid was further dried under vacuum at 60-65°C for 14 to 15 hours to yield 11.5 g of esomeprazole magnesium of amorphous form.

Example 3

Esomeprazole magnesium trihydrate (10g) was dissolved in a mixture of dichloromethane (50 ml) and ethanol (70ml) at 25-30°C. Any undissolved material was filtered off. The clear solution thus obtained was subjected to spray drying with an inlet temperature of 70-80°C and an outlet temperature of 22-42°C. The solid was further dried under vacuum at 60-65°C for 14 to 15 hours to yield 5.82 g of esomeprazole magnesium of amorphous form.

Example 4

Esomeprazole magnesium trihydrate (100g) was dissolved in methanol (1000ml) at 25-30°C. Any undissolved material was filtered off. The clear solution thus obtained was subjected to spray drying with an inlet temperature of 65-68°C and an outlet temperature of 22-42°C. The solid was further dried under vacuum at 60-65°C for 14 to 15 hours to yield 55 g of esomeprazole magnesium of amorphous form.

CLAIMS:

1. A process for the preparation of amorphous form of esomeprazole magnesium which comprises recovering amorphous esomeprazole magnesium from a solution thereof in a suitable solvent by spray drying.
2. The process according to claim 1 wherein esomeprazole magnesium is obtained as a solution in a suitable solvent, directly from a reaction mixture.
3. The process according to claim 1 wherein esomeprazole magnesium solution is obtained by dissolving crystalline esomeprazole magnesium in a suitable solvent.
4. The process according to claim 1 to 3 wherein suitable solvent is selected from the group consisting of alcohols, halogenated hydrocarbons, nitriles, cyclic ethers, and mixtures thereof.
5. The process according to claim 4 wherein the alcohol is selected from the group consisting of methanol, ethanol, isopropanol, and mixtures thereof.
6. The process according to claim 4 wherein the halogenated hydrocarbons is selected from the group consisting of dichloromethane, dichloroethane, dibromoethane and mixtures thereof.
7. The process according to claim 4 wherein the nitrile is acetonitrile.
8. The process according to claim 4 wherein the cyclic ether is selected from the group consisting of tetrahydrofuran, dioxane and mixtures thereof.
9. The process according to claim 1 wherein an organic amine or ammonia is added to the solution of esomeprazole magnesium.
10. The process according to claim 1 wherein an organic amine is diethylamine, triethylamine, and mixtures thereof.
11. The process for the preparation of amorphous form of esomeprazole magnesium substantially as herein described and illustrated by the example herein.

Dated this 18TH day of **October, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

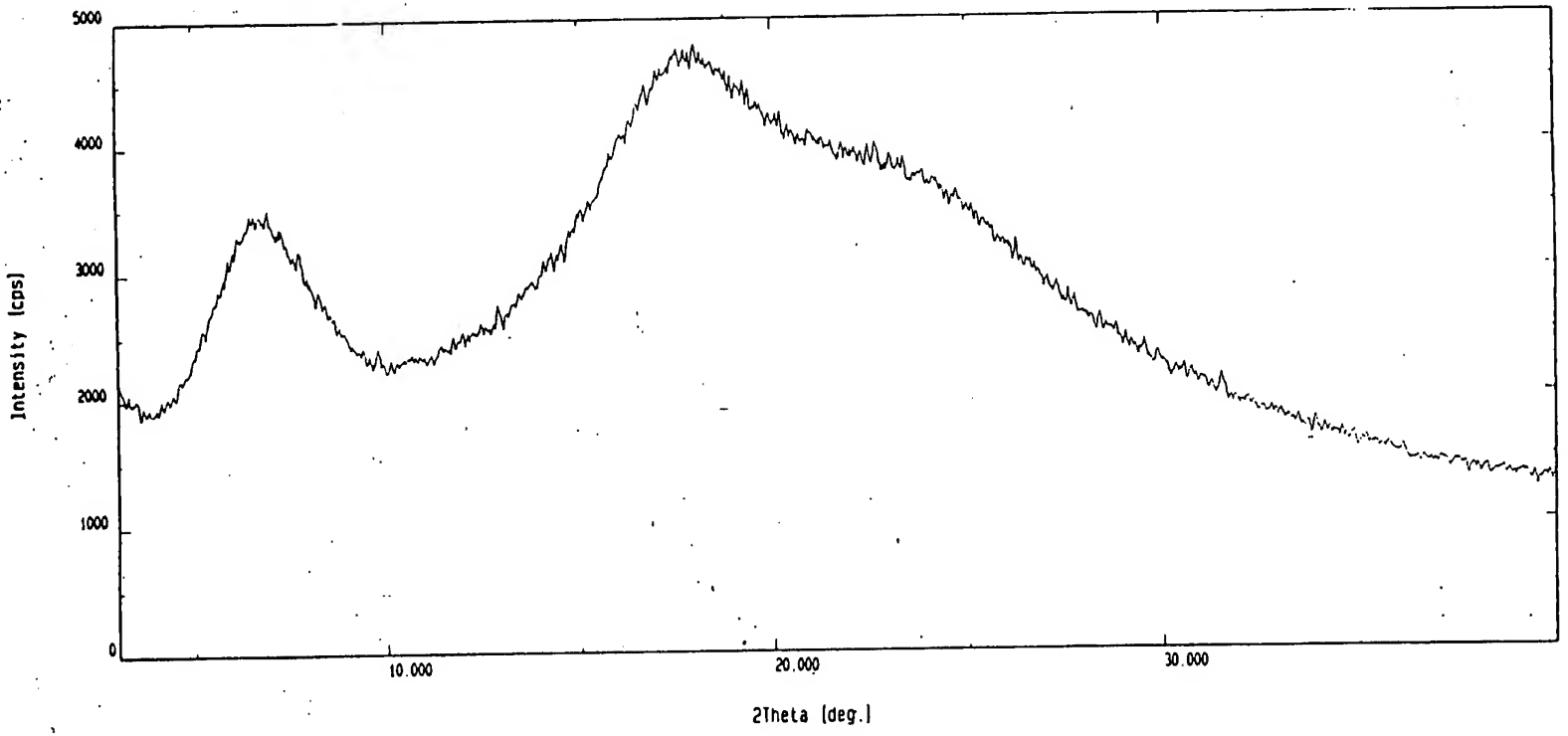
No. of sheets = 02

DUPLICATE

Application No.

Sheet 01 of 02

Figure – 1



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

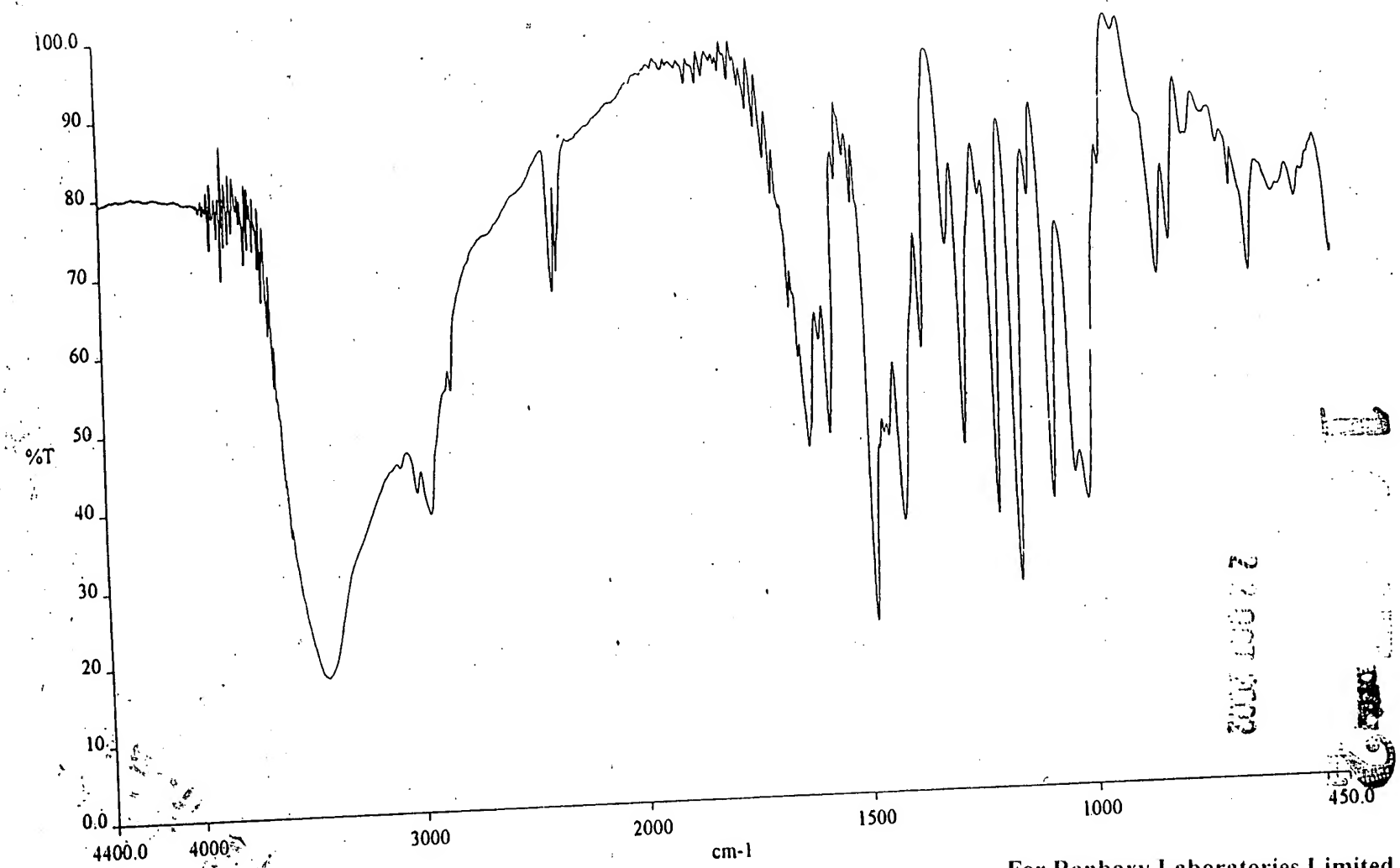
Ranbaxy Laboratories Limited

No. of sheets = 02

Application No. 1057/Del/02

Sheet 01 of 02

Figure – II



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary